Response to Comments on Toxicological Issues related to Benzene submitted by the American Petroleum Institute (API) (Set 2).

Comment 1: Executive Summary. This review evaluates the epidemiological evidence cited in the benzene component of the report, which is found in Appendix B of the March 21 document. Those portions of the exposure and toxicology sections that impact interpretation of the human data will also be discussed. General comments on the report are presented first, followed by a discussion of the epidemiological evidence.

The authors of the OEHHA document provide essentially no evidence that direct childhood exposures to benzene influence either adult or childhood leukemia risk. The only evidence cited in support of this hypothesis are two relatively crude community-based studies that suggest possible associations with petroleum fuels and/or combustion products. However, these studies can do no more than suggest speculative hypotheses that need to be confirmed through more rigorous research designs. Furthermore, the authors of the OEHHA document do not present the results of other research that fails to support this hypothesis.

The OEHHA document also fails to provide convincing evidence that parental exposure to benzene is associated with childhood leukemia. Only four dated, case-control studies are presented, all of which have considerable potential for bias that might have produced spurious associations. Furthermore, a wider search of the literature identified four additional case-control studies addressing benzene exposure that did not report significantly increased associations. This included two very large (> 1000 case) studies that found no association.

Overall, the reviewed studies provide no evidence whatsoever for an association between parental benzene exposure and childhood ALL, which is the predominant leukemia subtype (i.e. 56-88% of cases in the reviewed studies). One cannot completely discount a possible association between maternal exposure during pregnancy and ANLL, given that Shu et al. (1988) reported a significantly increased four-fold (95% CI 1.8-9.3) association with maternal benzene exposure (based on 11 exposed cases and 21 exposed controls) and a significantly increased two-fold

association with gasoline exposure. However, no conclusions on the causal relationship between benzene and ANLL can be drawn from this single study, especially given that other studies have reported conflicting results. Buckley et al. (1989) found that ANLL was not significantly associated with maternal occupational exposure to solvents or petroleum products and Raashou et al. (2001) found no significantly increased association between community benzene exposure during pregnancy and ANLL.

General Comments. The authors present an incomplete and selective review of the literature. Only four case-control studies of parental exposure are reviewed (Shaw, 1984; Shu, 1988; Buckley, 1989; McKinney, 1991). The authors state that this scant literature provides "a significant amount of evidence to suggest that exposure to benzene is associated with childhood leukemia". However, they give no indication that they searched the wider literature to evaluate the consistency of the body of evidence on this topic. We performed a cursory Medline search that identified four additional case-control studies addressing parental exposure to benzene, none of which found a significantly increased risk (Lowengart, 1987; Feingold, 1992; Kaatsch, 1998; Shu, 1999). These four studies will be discussed in the section reviewing the epidemiological evidence specifically.

Response 1: OEHHA thanks the API for identifying additional studies not cited in the draft. It should be noted that in all occurrences, OEHHA described the evidence of benzene and childhood leukemia as suggestive. OEHHA believes that a causal relationship based on the epidemiological evidence would be difficult to establish at this time. However, OEHHA took a more comprehensive approach, examining both the available human and animal studies. Examination of the overall weight of evidence is stronger compared to examination of the human data alone. As noted in the draft document, Maltoni et al. (1983; 1985; 1989) reported an enhanced carcinogenic effect of benzene was observed in animals when treatment was started in embryonic life and that higher tumor incidence was observed when animals were exposed in utero than in animals exposed when mature.

Comment 2: The authors of the OEHHA document were also selective in the way study findings were presented and interpreted. They reviewed the studies relatively uncritically, embracing findings and interpretations that support an association between parental exposure to benzene and childhood leukemia, while not discussing conflicting results, potential biases, or alternative interpretations.

An example of selectivity can be found in their review of the evidence on paternal exposure to benzene. Shaw et al. (1984) failed to find an association between paternal exposure to benzene and leukemia, which the OEHHA report ascribes to less precise exposure assessment than McKinney et al. (1991). However, the report does not discuss the greater potential for recall bias in McKinney et al. (1991) compared to Shaw et al. This limitation of the former study could easily have produced a spuriously increased association. Shaw et al. estimated benzene exposure by linking the National Occupational Hazard Survey to the paternal occupation listed on the birth certificate, creating an imprecise but objective measure of occupational exposure near the time of birth. McKinney et al. based exposure to individual chemicals on parental recall of workplace or household exposures, which is a highly subjective estimate of exposures that occurred many years in the past. The impact of recall bias, which is a potential problem in almost all of the reviewed literature, will be discussed in more detail later.

Another example of selective interpretation can be found in the review of Buckley et al. (1989). The OEHHA report indicates that Buckley et al. found a greater association between petroleum products and leukemia when maternal occupational exposure occurred during pregnancy, compared to either pre-conception or postnatal exposure. This finding appears to support an in-utero effect from benzene exposure. However, although the odds ratio (OR) was slightly higher during pregnancy (2.8 vs. 1.6-2.0), Buckley et al. state that exposures during these different time periods are highly correlated and that "it was not possible to pinpoint the period in relation to the pregnancy when exposure gave the greatest increase in risk". In this particular instance, the OEHHA authors draw a conclusion that is not supported by the study data and is directly contradicted by the original authors."

Response 2: OEHHA developed this document in a restricted timeframe and did not provide a complete and detailed analysis of the available data Instead, we focused on the issue at hand. For these reasons, OEHHA utilized, where possible, previous efforts to review the benzene literature (OEHHA, 1997; 2000). The draft was not intended as a selective review of the literature, as both positive and negative epidemiological studies were described. However, where any unintended mischaracterizations are identified, these will be corrected in the final version

Comment 3: The authors of the OEHHA report misrepresent or misinterpret recent findings by the National Cancer Institute (NCI) on childhood cancer incidence. The OEHHA authors state that "the incidence of leukemia among children ... increased by about one percent per year over the last 20 years, which is driven primarily by increases in acute lymphatic leukemia". This implies a steady increase in leukemia, which these authors then suggest may be at least partly due to in-utero exposure to carcinogens However, researchers at NCI actually concluded that rates for the major pediatric cancers have remained fairly stable since the 1970s, except for modest increases caused by improvements in diagnosis or changes in reporting. For leukemia, SEER data suggest a step-wise increase in incidence during approximately 1982-1985, with stable rates before and after this period (Linet, 1999). Such step-wise increases are consistent with discrete diagnostic improvements/changes, not with the cumulative effect of chemical exposures. The authors of the OEHHA report also fail to consider the fact that occupational and ambient benzene levels have fallen considerably during the time of this purported leukemia increase.

Response 3: OEHHA agrees that the NCI (Linet et al., 1999) analysis suggests a step-wise increase in childhood leukemia incidence during the early 1980's. OEHHA will revise the draft to reflect the Linet (1999) analysis and will compare the temporal trends in benzene concentrations and leukemia rates by age.

Comment 4: There are several other factual errors in the OEHHA document that detract from reader confidence in the report. For example, the authors state that there are statistically significant elevations for maternal exposure to solvents or petroleum products in Buckley et al. (1989), when these elevations are actually for paternal exposure. The authors also state that Knox and Gilman (1997) studied "22,458 children who died from leukemia", which is incorrect. Knox and Gilman (1997) evaluated all childhood cancers combined. Leukemia makes up only about one third of the childhood cancers in the US and Britain, so most of the cancers investigated by Knox and Gilman (1997) were not leukemias."

Response 4: OEHHA thanks the commenter for pointing out these errors. We are in the process of correcting these errors in the revision of the draft report.

Comment 5: The OEHHA report includes a strong statement in the *Summary of potential differential effects* (p.2) that "additional evidence suggests that childhood exposures to benzene may result in higher lifetime risk of leukemia than equivalent adult exposures". On page 4 they again state that there is "evidence to suggest that children or the developing fetus exposed to benzene may exhibit a higher lifetime risk of cancer". They further indicate that "one must be mindful throughout the discussion of the evidence that benzene exposure early in life may increase lifetime ... leukemia". This statement is also reiterated in the conclusion. However, the section on *Childhood exposures resulting in increases in adult-onset leukemia* is limited to the single statement that "there are no human studies available that have examined childhood exposures to benzene and increases in **lifetime** risk". One can only wonder why the authors would repeatedly make a statement for which they themselves acknowledge no supporting evidence.

Response 5: The commenter is correct that there are no human data available that examine benzene exposure early in life and increased lifetime risk of leukemia. However, there are data from animal studies and from human studies of age-specific excess leukemia risk following exposure to ionizing radiation exposures that primarily form the bases of the above statements. For example, as described in the draft Section V.B: "Cancer rates in the offspring were compared

to control animals and to their dams, who were exposed to the same concentration of benzene for the same period. Although no statistical analysis was reported, the authors stated that "an enhanced carcinogenic effect of benzene was observed in animals on which treatment was started during embryonal life" and that animals whose exposure began *in utero* had higher incidences of some tumor types than the breeders exposed only as adults (Maltoni et al., 1983; 1985; 1989) (Table 1)." These findings are also supported by animal studies of transplacental genotoxicity and transplacental altered hematopoiesis, which are potentially important mechanistic evidence.

As noted in the draft, similar temporal patterns are observed in human populations for leukemias induced by ionizing radiation, chemotherapeutic agents, and benzene. For example, the pattern of risk for leukemia from exposure to ionizing radiation follows a wave like pattern, rising within 5 years after exposure and then returning to near baseline rates within 30 years (NRC, 1990). Observations of secondary leukemia following exposure to several classes of chemotherapeutic agents (Brusamolino et al., 1998; Larson et al., 1996), and of leukemia following exposure to benzene in the workplace (Hayes et al., 1997; OEHHA, 2000; Finkelstein, 2000), are consistent with the pattern observed for radiation cohorts. It should be stressed that this radiation-induced pattern of risk has been used by several groups of researchers to adjust or weight exposures of benzene when conducting risk assessments of benzene (Crump and Allen, 1984; Thorsuland et al., 1988; Crump, 1994; OEHHA, 2000). Indeed, the regulatory cancer potency estimates for benzene, which have been promulgated and used on the state and federal level for decades, were weighted based on the pattern of leukemia risk observed among radiation-exposed cohorts. With respect to differential sensitivity of children and adults to leukemia induction, the draft states: "Although we do not have information on benzene-induced leukemia for early life exposures, we do have such data from atomic bomb survivors and other radiation-exposed cohorts. Interestingly, as shown in the Figure below, exposures that occur early in life and late in life confer greater excess risk than exposures between the ages of 20 and 45." Benzene-exposed cohort studies, which form the basis of regulatory cancer potency estimates, were of workers generally of ages 20 to 55. Thus, if the increased sensitivity of children relative to working-age adults to radiation-induced leukemia is operative for benzene-induced leukemia, then current cancer potency estimates for benzene may not adequately capture lifetime leukemia risk.

Comment 6: "The OEHHA authors suggest that there is both toxicological and epidemiological evidence that benzene causes childhood leukemia. Yet, the toxicological mechanisms that they propose would seem to argue against the epidemiological evidence, and vice versa. The authors state that "there is strong evidence that metabolism plays a critical role in benzene toxicity" and that toxic oxide or oxepin metabolites are generated primarily by cytochrome P450 isozymes. The authors further state that CP450 activity is greatly reduced/limited during the first few weeks of life and, one assumes, during gestation as well. However, the authors also state that the limited epidemiological evidence suggests an effect from pre-natal maternal exposure, which would be unlikely given reduced metabolic activation in the fetus."

Response 6: Although fetal or neonatal oxygenase activities are underdeveloped, the corresponding Phase II (detoxification) enzyme systems are even less active relative to the adult. Illustrations of this point can be found in descriptions of enzyme activities, toxicity, and DNA adduct formation in fetal or neonatal rodents cited in the SB25 summaries on benzo[a]pyrene and other PAHs

As noted in the draft, a detailed study is needed to predict the metabolism and distribution of toxic metabolites in the fetus and infant relative to the adult. Such an effort would need to consider transfer of maternal-form metabolites to the fetus in addition to the inherent metabolic capabilities of the fetus.

The pharmacokinetics of metabolism in the fetus and neonate is complicated by the appearance and then disappearance of fetal isoforms of cytochrome P450, and the appearance of adult isoforms. The capability of these various isoforms for metabolizing benzene to toxic metabolites is not characterized.

Comment 7: The authors further suggest that paternal or maternal pre-conception exposures may be important. This requires an entirely new mechanism based on germ-cell damage. As support for this hypothesis, the authors cite toxicological evidence for sperm damage in animals

exposed to high levels of benzene. However, they provide no evidence that sperm damage would result in increased cancer incidence among offspring, rather than decreased fertility or early (i.e. unrecognized) spontaneous abortion, or that benzene-induced germ-cell damage would produce the same type of cancer as caused by direct exposure to somatic cells. The authors appear to be presenting multiple, often contradictory mechanisms in an attempt to create the appearance of scientific support."

Response 7: Observations of germ cell mutations among benzene-treated rodents is consistent with a genotoxic mode of action for preconceptional carcinogenesis, as has been suggested by some epidemiological studies of benzene. The commenter is correct to point out that the doses used in the animal studies were high. OEHHA agrees that the data are suggestive and not conclusive. However, the statute requires OEHHA to list TACs that "may cause infants and children to be especially susceptible to illness". We have presented the evidence as suggestive and agree that it is relatively weak. However, we cannot ignore the evidence and believe it is worthwhile presenting and discussing the evidence in light of this statute.

Comment 8: "The authors of the report repeatedly cite the evidence for leukemia from ionizing radiation, as support for an effect from low-level benzene exposure. However, they provide no real evidence that exposure to radiation produces the same effects as exposure to benzene, with the exception of some temporal similarities in descriptive epidemiology. Even here, the data presented are from an NRC report on exposure to ionizing radiation, not benzene. The authors need to provide mechanistic evidence of similar effects following exposure to ionizing radiation and benzene, in order for this comparison to be meaningful."

Response 8: Patterns of radiation-induced leukemia have been used for decades to estimate the risks of benzene-induced leukemia, including the cancer potency estimate forming the basis of the current California TAC for benzene. See response 5.

Comment 9: The authors cite three case-control studies that demonstrated a positive association between parental occupational exposure and childhood leukemia (although only two studies presented results specific to benzene) and only one that demonstrated no association. This is presented as "considerable evidence ... that benzene causes childhood leukemia". As will be discussed later, such a small body of studies with considerable potential for bias hardly represents "considerable" causal evidence. Furthermore, the authors have failed to consider other studies or the impact of "publication bias" on this body of literature".

Publication bias" is the tendency for studies showing significant associations between exposure and disease to be preferentially published, both because editors and reviewers favor positive (i.e. "interesting") results and because authors recognize this bias and tend to pursue publication of positive findings and to thoroughly "mine" data for positive results. Also, within any particular article, authors are more likely to present the positive findings and may tend to omit "uninformative" negative/null results. Publication bias is recognized as a serious problem in randomized drug trials (Dickersin, 1987; Dickersin, 1990; Easterbrook, 1991) and appears to be a problem in the epidemiological literature as well (Higginson, 1987; Dickersin, 1992). Subsequently, the epidemiological literature would be expected to contain more positive studies than negative (i.e. null) ones, simply as an artifact of this bias.

Examples of possible publication bias can be found within the four studies themselves. Buckley et al. (1989) solicited information on exposures to benzene and other individual chemicals, but presented tabular results only for exposure categories (e.g. solvents). Specific results for individual chemicals were not discussed, except where they demonstrated a significant positive effect (e.g. polystyrene). Furthermore, in an attempt to discount recall bias, Buckley et al. indicate that they have not found elevated risks from "chemicals such as pesticides" in similar studies of childhood cancer that they have performed. These negative results are not presented or cited, suggesting that they have not yet been published and that these results would be omitted from any review of the published literature.

Response 9: OEHHA thanks API for this analysis. OEHHA agrees that there are many limitations to the epidemiological literature including possible publication bias. However, no

evidence of publication bias has been provided by the commenter. As stated above, OEHHA took a weight-of-evidence approach to the issue by including both the suggestive evidence in human studies and the animal evidence. See response 1.

Comment 10: The OEHHA report presents information on ambient exposures, but does not contrast these to occupational levels. Furthermore, none of the cited studies provide any information on occupational levels. One is left to wonder if current ambient levels less than one ppb would have any measurable effect on children's health, given that no human health risks have been convincingly demonstrated from occupational exposures three or more orders of magnitude higher (i.e. current OSHA PEL of 1 ppm).

Response 10: Comment noted. Both OEHHA (2000) and U.S. EPA (1998) evaluated the available evidence pertaining to low dose linearity and applied that evidence to criteria in the carcinogen guidelines for selecting among linear and non-linear approaches. Since the mechanism of benzene-induced carcinogenesis remains unclear and since a significant amount of information suggests that benzene induces leukemia in a dose-response relationship that is linear to low doses, both agencies concluded that sufficient evidence does not exist to move away from a linear approach.

Comment 11: Comments specific to the epidemiological literature. "The OEHHA report provides brief summaries of the cited literature, but no real critical evaluation. This section of our review evaluates the limitations of the cited literature and discusses the results of additional studies that were not cited in the OEHHA document.

11-1) Recall bias. A major limitation associated with three of the case control studies is a strong potential for recall bias (Shu, 1988; Buckley, 1989; McKinney, 1991). Recall bias is a problem when individuals with serious illnesses are asked to recall past exposures. These patients and their surrogates (e.g. parents of afflicted children) often recall past exposures more vividly than healthy persons, because of a strong stimulus to identify/understand past exposures that may

have contributed to their illness. The potential for recall bias is greatest for dreaded illnesses (e.g. cancer) and for potentially hazardous exposures that are well publicized (e.g. radiation, benzene, and asbestos). It is exacerbated when individuals are asked to recall exposures many years in the past. The increased ability to summon up memories among the cases, compared to the controls, generally results in spuriously elevated odds ratios.

Several of the characteristics of the cited studies make recall bias especially likely. These include:

- Childhood leukemia is a particularly traumatic and dreaded disease that likely provides a strong stimulus for parental recall. Parents of afflicted children could be expected to have spent long hours trying to recall past events that might have triggered this illness in their child.
- All controls represent healthy children drawn from the general population. These parents would have no consistent stimulus for pondering past occupational exposures.
- All parents were asked to recall prenatal exposures up to 15-20 years in the past. Differential recall between cases and controls tends to become more pronounced over longer time intervals.

It is interesting to note that no association with childhood leukemia was found in the only study to use a relatively objective estimate of benzene exposure (Shaw, 1984).

Two of the studies attempted to explain away the potential effect of recall bias. McKinney et al. (1991) indicated that although recall bias was possible, it was unlikely to have a big impact because similar elevations were not seen across all temporal periods (pre-conception, conception, postnatal). Buckley et al. (1989) also discounted recall bias because "no systematic differences in response were found for the vast majority of questions asked" and because they had not found a consistent effect from self-reported chemical exposures in previous research, although these previous results were neither cited nor presented. These are speculative arguments that do little to reassure the reader that recall bias has been avoided.

The McKinney et al. study was performed in an area of the UK where there had been several years of media attention and litigation regarding a high-profile cluster of childhood leukemia

cases (i.e. the Seascale cluster). It is reasonable to expect case fathers to have seen reports alleging damaged sperm from chemical/radiation exposure. These men may have been well "educated" that only paternal occupational exposures prior to conception could be of importance to childhood cancer development. In fact, it is likely that there was media attention surrounding a contemporary study in the same general location that reported an association with pre-conception exposure (Gardner, 1990). The rationale used by Buckley et al. to discount recall bias ignores the fact that biased recall should logically be most prominent for odiferous or well-publicized hazards (e.g. benzene and other solvents), not all exposures.

Response 11-1: OEHHA agrees that recall bias is a problem in these types of studies. The commenter notes that no association with childhood leukemia was found "in the only study to use a relatively objective estimate of exposure to benzene (Shaw et al., 1984). The authors of this study note that the small sample size (255 cases) and exposure misclassification were problematic. The exposure classifications were based on whether the father had a job with "potential exposure" to benzene. It is unclear why the commenter thinks the exposure measure in Shaw et al, 1984, were more objective than in other studies.

Buckley et al. (1989) conducted a case-control study of occupational exposures of parents of 204 children with acute nonlymphoblastic leukemia. Controls were matched by date-of-birth and race. Paternal exposure to solvents (OR 2.1; p=0.003) and petroleum products (p=0.002) were more common for cases than for controls. The comment concerns the impacts of recall bias on the positive results of the study. McKinley et al. discuss recall bias in their report due to the concern that parents of cases may have better recall of past exposures or to exposures linked to leukemia in particular. They state that "the effect of any nonspecific recall bias must be small since no systematic differences in response were found for the vast majority of questions asked. These questions included exposures to solvents, degreasers, cleaning agents, plastic monomers, paints, pigments, oil or coal products, a variety of metals, insulation materials, nonionizing radiation, and many other substances or agents. One might expect positive bias of reporting exposures to a number of the groups of "toxic" materials, not just a couple of the groupings.

McKinney et al. (1991) conducted a case-control study including 109 cases of childhood leukemia or non-Hodgkin's lymphoma and analyzed associations between parental occupational exposures and risk. Interviews of case and control parents were conducted by trained interviewers. A complete occupational history of the parents was taken including exposure to specific substances and radiation. The most striking association of all studied in the paper is that of preconceptual paternal exposure to benzene and childhhood leukemia or non-Hodgkin's lymphoma (OR 5.81 (95% CI 1.67 – 26.44). The comment notes that recall bias may have impacted the results. However, McKinney et al. note in their paper that:

> "differential recall of information between case and control parents can always be cited as an explanation for significant positive results. Parents of children with leukemia might be expected to over-report exposures, especially to the known leukemogens benzene and radiation. Certain features of the current results, however, suggest that recall bias is unlikely. If recall bias were strongly influencing the interview responses a similar number of excesses might be expected for both mothers and fathers across the three periods of exposure. This is not the case in either instance and suggests that recall bias is not operating strongly in our dataset" "The results for fathers' exposures during the preconceptual period cannot be explained by recall bias resulting from publicity after publication of work by Gardner et al. as all interviewing was completed before the paper's publication."

11-2 Multiple exposures. Workers in the four cited studies were exposed to a variety of chemicals simultaneously. These exposures are often highly correlated, making it difficult or impossible to tease out the effect of individual exposures or even exposure classes. Statistical adjustments for multiple exposures are of limited utility when exposures are highly correlated, especially when there are small numbers of exposed subjects.

Response11-2: OEHHA agrees that multiple exposures really make finding an association difficult.

11-3) Confounding. Another major limitation of the four cited studies is the lack of control for potentially important confounding factors. Two studies made an attempt to control for a few demographic factors and/or other occupational exposures (Buckley, 1989; McKinney, 1991), but only Shu et al. (1988) developed logistic models that simultaneously adjusted for a substantial number of potential risk factors. None of the studies presented results for potentially important personal behaviors, such as cigarette smoking, or adjusted for them in the analyses.

Although smoking has not been conclusively established as a risk factor for childhood cancer, tobacco smoke contains numerous known carcinogens and other chemicals, including pesticides and solvents. Some investigators have also observed a positive association between cigarette smoking and adult leukemia (Kinlen, 1988; Mills, 1990; Siegel, 1993). Failure to statistically adjust for smoking leaves the reader wondering if tobacco smoke exposure could have confounded the benzene-specific findings. If adjustment was not performed because no positive associations between parental smoking and childhood leukemia were found, then one is left to wonder if it is consistent to expect increased childhood leukemia risk from parental occupational exposures to similar chemical constituents.

Response 11-3: OEHHA agrees that correcting for confounders in epidemiological studies is important. Generally, one would account for radiation exposure if studying leukemia since that is a known strong risk factor. However, the example given in the comment of a confounder is that of parental cigarette smoking. As the comment points out, parental smoking has not been established as a risk factor for childhood leukemia. Thus the potential for confounding is not known, although it may in fact exist. In addition, Shu et al. (1988), who report an association with maternal benzene exposure and acute nonlymphocytic leukemia in their children, note that the vast majority of mothers did not smoke and that the percent of smoking fathers in cases and controls were the same.

11-4) Inconsistent/conflicting results. The authors of the OEHHA document do not discuss the conflicting results across the four case-control studies. They point to McKinney et al. (1991) as evidence for an increased association between paternal benzene exposure and childhood leukemia and acknowledge that Shaw et al. (1984) found no such association. However, they

fail to note that Shu et al. (1988) also found no association, reporting that "paternal occupations during pregnancy seemed to have no influence on the occurrence of leukemia". This finding is particularly noteworthy given that Shu et al. (1988) studied workers in Shanghai China, where benzene is widely used and where many occupational exposures have routinely exceeded 30-40 ppm or higher (Yin, 1987; Dosemeci, 1994; Budinsky, 1999; Wong, 1999). Shu et al. (1988) did find a significantly increased association between maternal exposure and acute non-lymphocytic leukemia (ANLL), but not for the more common acute lymphocytic leukemia (ALL).

"Buckley et al. (1989) reported significant associations between childhood ANLL and paternal exposures to "solvents" or "petroleum product", but no significant results/trends for maternal exposure to these general chemical/hydrocarbon categories. These authors reported no benzene-specific results, even though benzene-specific exposure information was sought, suggesting either that no obvious association was noted or that small numbers precluded chemical-specific findings. A recent NCI review of the literature "did not find compelling evidence" for an association between paternal hydrocarbon exposure and childhood leukemia (Colt, 1998), suggesting that the findings by Buckley et al. are not consistent with the wider literature. Therefore, only one study appears to report a clear association with paternal exposure to benzene and one study a clear association with maternal exposure. This hardly represents "considerable" or "significant" evidence for an association with childhood leukemia.

Response 11-4: OEHHA recognizes that the epidemiological findings are not all consistent. The difficulties in evaluating the impact of parental benzene exposure on incidence of childhood leukemia in the offspring are tremendous. Nonetheless, one cannot ignore positive results in some studies because of negative results in other studies. As noted in the comment, Shu et al (1988) found that maternal exposure to benzene was associated with increased incidence of acute non-lymphocytic leukemia in the offspring (OR = 4.0; 95% CI = 1.8 to 9.3). In addition, they also found that maternal gasoline exposure was associated with increased risk of acute lymphocytic leukemia in the offspring (OR = 1.7; 95% CI = 1.0 to 3.0). McKinney et al. (1991) found that paternal exposure to benzene was associated with elevated risks of childhood leukemia and non-Hodgkin's lymphoma (OR = 5.81; 95% CI = 1.67-26.44). It is difficult to discount these positive results on the basis of negative results in other analyses. OEHHA has

tried to word the draft document carefully, acknowledging that the evidence is suggestive rather than "conclusive" of an impact of parental exposure on benzene risk in the offspring. We will remove the word "considerable" in front of evidence during the revision of the draft document.

"**11-5)** Poor exposure metrics and lack of dose-response. None of the reviewed studies generated quantitative exposure metrics for individuals (e.g. ppm or ppm-years). Instead, parents were placed into qualitative, dichotomous (i.e. yes/no) exposure categories. Traditionally, the misclassification introduced by such crude exposure metrics has been thought to bias OR toward the null. However, more recent evidence has suggested that there are many circumstances where this is not necessarily the case (Dosmeci, 1990; Flegal, 1991; Wacholder, 1995). In fact, Maldonado et al. (2000) performed a sensitivity analysis and found that "several approximately nondifferential exposure-misclassification scenarios would have resulted in substantial error away from the null". Therefore, one is probably safe in assuming that the bias introduced by this misclassification might be in any direction (toward or away from the null).

Another problem with such dichotomous exposure metrics is that they do not allow determination of dose-response relationships. Among the four case-control studies, only Buckley et al. (1989) provided any dose-response evaluation, based on the crude metric of "days of exposure". These authors reported a monotonic dose-response trend for paternal exposure to petroleum products and maternal exposure to paints, but not for paternal exposure to solvents.

Among the four studies identified in our recent search of the literature, Lowengart et al. (1987) noted a monotonic trend for paternal exposure to spray paints, but an inverse relationship for maternal or paternal exposure during pregnancy, with marginally protective OR associated with exposures greater than once per week. Shu et al. (1999) reported OR for maternal solvent exposure that were substantially higher for those exposed for less than the median duration compared to those with greater than median exposure.

The few monotonic trends reported in the reviewed studies may have been the result of chance, post hoc manipulation of exposure cut points, or recall bias. A finding reported by Feingold et al. (1992) supports the argument for recall bias causing a spurious monotonic trend. These

authors reported an association with parental exposure to asbestos and both childhood brain cancer and ALL, "with stronger associations for high as compared to medium linkage levels." Asbestos should not produce cancer in offspring, given that these fibers act through physical irritation at the site of contact. However, asbestos is a well-publicized hazard that might stimulate biased recall, with the greatest effect among those with the highest exposure. Aromatic hydrocarbons might be expected to have a similar effect.

Response 11-5: The problem of estimating exposure is endemic in epidemiology studies. It does not mean that positive associations are therefore all wrong. This draft OEHHA document did not attempt to quantify risk, as that was not the purpose, but rather was focused on identifying hazard. However, despite the recent counterexample in the abstract by Maldonado et al (2000), exposure misclassification generally biases towards the null because you dilute exposed people with unexposed people and therefore reduce the power of the study to detect an effect.

11-6) Multiple statistical comparisons. These studies explored many different occupational exposures, usually with no clear a priori focus on benzene. McKinney et al. (1991) state that they evaluated 480 statistical comparisons, which gives some indication of the exploratory nature of this type of research. These multiple, post-hoc statistical comparisons would be expected to produce a substantial number of statistically significant chance findings (e.g. on average, 24 of 480 comparisons would be statistically significant by chance). Given benzene's high profile as a leukemogen, chance elevations for benzene would probably be reported/highlighted more often than for less "plausible" exposures, enhancing the effect of publication bias.

Response 11-6: OEHHA notes the comment. We agree that multiple comparisons increase the chance of finding a false positive result beyond the p level for a single study. However, it should be noted that in McKinney et al (1991) preconceptual paternal exposure to benzene and radiation, both leukemogens, had the strongest associations with childhood leukemia risk in the offspring than any other exposure, and most of the rest had no association. The comment regarding publication bias is speculative and no evidence that there was substantial publication bias is presented.

11-7) Additional case-control findings. A cursory search of Medline identified four additional case-control studies and one cohort study that addressed parental occupational exposures to benzene. In a Denver-area study, Feingold et al. (1992) were able to evaluate only paternal benzene exposure in relation to ALL, because of small numbers of exposed case mothers. These authors reported a slight, non-significant benzene-specific OR of 1.6 (95% CI 0.5-5.8). There were also slight to moderate, non-significantly increased OR for some petroleum products.

Lowengart et al. (1987) reported no benzene-specific results, but stated that none of the "other" paternal or maternal exposures about which they inquired (including benzene) were significantly associated with leukemia. However, these results are based on only 123 case-control pairs, so one cannot rule out a non-significantly elevated risk from benzene exposure. Paternal occupations within the "petroleum-chemicals" exposure category was associated with an OR of 1.0 (0.33-3.06). Paternal or maternal home exposures to petroleum products greater than once per week during pregnancy were associated with ORs of 0.7-0.8. Positive associations were reported for exposures to spray paints and several chlorinated solvents (e.g. CCl_4).

Kaatsch et al. (1998) did not present benzene-specific ORs in this report of their large, German case-control study. However, they stated that no association was found for occupational exposure to plastics, resin fumes, or benzene. The very large sample size of this study (>1000 cases) suggests that these investigators were unlikely to miss a moderate association by chance.

Shu et al. (1999) studied more than 1800 ALL cases matched to over 1900 controls. These individuals were identified through the Children's Cancer Group, a cooperative clinical trials group within the US and Canada. This appears to be the same clinical group used to identify cases and controls for Buckley, et al. (1989). Overall, Shu et al. (1999) found no association between ALL and either maternal or paternal benzene exposure. They reported maternal benzene-specific OR of 0.5-0.7 across all temporal periods related to conception. All upper confidence limits were 1.8 or less. Statistically significant ORs of 1.6-2.4 were reported for maternal exposure to "solvent" or "paint/thinner" before or during conception, but solvent risk was limited to those mothers with less than the median duration of exposure. The ORs for any

maternal exposure to "oil or coal products" were approximately 1.0. There were no increased paternal associations except for a moderately increased association with pre-conception plastic exposure (OR 1.4, 95% CI 1.0-1.9). The ORs for paternal exposure to benzene were 1.0-1.2.

The cohort study followed over 200,000 Swedish children born near the time of two censuses. Paternal exposure was estimated from occupations/industries listed on the census form. Chemical-specific analyses were hindered by small numbers of leukemia cases, but RR for probable/possible occupational exposure to oil, general chemicals, solvents, and benzene were 0.93 (95% CI 0.5-1.72), 0.47 (0.25-1.29), 1.25 (0.8-1.95), and 1.23 (0.39-3.85) respectively. These results do not suggest a measurable leukemia effect from occupational exposure to benzene or petroleum products.

As with all epidemiological research, the above studies have limitations and even share some of the same potential biases of the other four case-control studies reviewed above. However, none of these additional studies support a convincing association between childhood leukemia and parental occupational exposure to benzene. These findings also call into questions the positive association with petroleum/hydrocarbon exposure reported in some of the original four studies. The large numbers and overall negative findings of the two most recent studies (Kaatsch, 1998; Shu, 1999) provide reassurance that a moderate effect of exposure was not missed due to chance.

Response 11-7: OEHHA thanks the commenter for references to negative studies that were not cited in the draft. As pointed out in the comment, the Feingold et al. (1992) and the Lowengart et al. (1987) studies both had small numbers of cases. Hence, they had very low statistical power to detect an effect. The numbers are even smaller for the Swedish cohort study (Feychting et al. 2001) published in February and mentioned in the comment. The authors point out that benzene exposure in their study is too rare to provide a meaningful result. However, the two large studies, each with more than a thousand cases, provide a serious question about the generality of previous results that suggest an effect of prenatal exposures of parents to benzene. Shu et al. (1999) considered only AAL; Kaatcsh et al. (1998) considered childhood leukemia. Still, both of these studies are subject to various potential sources of bias, one of which is recall bias. The commenter earlier pointed out the potential for cases being biased to over-report benzene

exposure because of its reputation as a toxic chemical. However, a bias could work the other way in that cases could tend to downplay their occupation as a source of benzene harming their child. Both these studies are also subject to the problem of multiple comparisons, noted earlier, perhaps explaining the rather incredible finding in Kaatsch et al. that maternal smoking is associated with a decline in childhood leukemia. Comments reflecting this analysis will be included in the final version of OEHHA's document.

11-8) Community study results. The authors of the OEHHA report cite community studies by Knox and Gilman (1997) and Nordlinder and Jarvholm (1997) as evidence supporting an association between childhood leukemia and exposure to gasoline or other petroleum-derived materials. As with the other studies in the report, results are summarized briefly and uncritically.

Knox and Gilman (1997) is just one of a series of community childhood cancer studies published in the *Journal of Epidemiology and Community Health* over the last several years by a group of investigators at the University of Birmingham, UK (e.g. Knox, 1995; 1996). These investigators have reported many associations between childhood leukemia and industrial facilities, waste sites, roads, etc. Some of these studies have been previously reviewed and have generally been found to be of poor quality, with numerous limitations, including crude and poorly described exposure metrics, uncontrolled confounding, multiple comparisons, and stronger conclusions than are supported by the data.

Knox and Gilman (1997) tried to identify geographical associations between various industrial/waste sites and all childhood cancer deaths in Great Britain during 1953-1980. The authors estimated "standardized density ratios" (SDR) for concentric rings around industrial facilities. These SDR compare case densities to estimates of the expected cancer mortality within the concentric rings. This is a very crude and non-standard methodology that has not been widely accepted among epidemiologists. Sir Richard Doll has been quoted as saying that this "is an extremely complex methodology and has not got a control ... There is no obvious connection between industrial sites and cancer" (*The Independent*, 1997). The authors generate a vast number of statistical associations based on proximity, with no link to personal exposures and with no control for possible confounding factors. To quote Professor Ray Cartwright of the

Leukaemia Research Fund, "We cannot accept this study as it is. You need to take individual people and look at their individual experiences" (*The Independent*, 1997). This type of research is not capable of identifying a common etiology for the polyglot of cancer types explored, and can do no more than suggest possible hypotheses that need to be confirmed using much more rigorous and well-accepted epidemiological approaches. A more detailed critique of Knox and Gilman (1997) is available upon request (Huebner, 1997).

Nordlinder and Jarvholm (1997) performed an ecological study correlating the leukemia rates in people < 25 years old with automobile density. They found a positive correlation between the number of cars/km^2 and acute myeloid leukemia (AML) rates, but not with other types of leukemia (e.g. ALL). Acute myeloid leukemia rates (per million person-years) were 3.4, 5.4, 5.4, and 5.5 for car densities of <5, 5-9, 10-19, and ≥ 20 cars/km^2, respectively. The authors correctly indicated that these results should be treated cautiously, because car density is a very crude surrogate for benzene/fuel exposure and because they did not control for group-level or individual-level confounding factors. Such group-level studies are subject to the ecological fallacy (i.e. group-level associations do not necessarily reflect associations at the individual level) and represent only crude, hypothesis-generating exercises.

As with the case-control studies, the OEHHA authors present only a selective review of the available community cancer studies. They discuss Knox and Gilman (1997), but fail to discuss a rebuttal article by Bithell and Draper (1995) that was highly critical of similar work by Knox in this area. They also present no studies with conflicting findings. For example, Alexander et al. (1996) found a statistically significant negative association between level of automobile ownership and childhood ALL (i.e. areas of England and Wales with lower levels of automobile ownership had higher ALL rates), providing indirect evidence against an association between childhood leukemia and community exposure to automobile fuels and/or combustion products.

Two very recent studies also failed to support a leukemia risk from community exposure to benzene. Reynolds et al. (2001) found no association between childhood leukemia and any measure of traffic exposure. Raaschou et al. (2001) used traffic patterns and street configurations to model the level of benzene exposure at the residences of approximately 1000

leukemia cases and 2000 controls in Denmark. They found absolutely no association with either traffic density or benzene exposure, with adjusted benzene OR of 0.8 and 0.4 for the highest exposure categories during pregnancy and childhood, respectively. These authors also reported that "the results showed no significantly increased risk of ... any of the morphological subtypes of leukemia (ALL, ANLL)...".

Response11-8: The comments about the two studies cited by OEHHA are noted. The draft document presents studies which suggest a possible relationship between exposure to benzene and childhood leukemia in the offspring. The comments also call our attention to two new traffic studies. The study of Reynolds et al. (2001) has very small numbers of cases; so it has little power to detect an effect. The study of Raaschou-Nielson et al. (2001) is much more substantial, with nearly 2000 cases. The comment notes that the study findings for childhood leukemia are not positive, but it does not mention the finding of a positive trend ($p = 0.06$) of lymphoma with benzene exposure. OEHHA will note this additional information in the final document.

11-9) Infectious etiology. The authors of the OEHHA report present none of the accumulating evidence that childhood ALL may be caused by an infectious agent (McMahon, 1992). Several British investigators have produced epidemiological evidence that population mixing in modern communities near industrial developments, military bases, nuclear reactors, etc. may predispose to childhood ALL through a rare response to some common, as yet unrecognized infection (Kinlen, 1990; Kinlen, 1997). This could explain the increased leukemia risks reported in some of the community cancer studies. There is even evidence that an infectious agent, promoted through population mixing, may have been the cause of the Seascale leukemia cluster (Dickinson, 1999). Sir Richard Doll has suggested that this is the probable explanation for this cluster (Doll, 1999), which formed the stimulus for the study by McKinney et al. (1991).

Response 11-9: The draft document is not a report on all the causes of childhood leukemia. It is a hazard identification report wherein we cite evidence suggestive of a potential effect of parental exposure to benzene and risk of leukemia in the offspring. In addition, we have not indicated anywhere in the report that benzene is the only or even the major cause of leukemia.

Comment 11-10: Summary and conclusions. The authors of the OEHHA document provide essentially no evidence that direct childhood exposures to benzene influence either adult or childhood leukemia risk. The only evidence cited in support of this hypothesis are two relatively crude community-based studies that suggest possible associations with petroleum fuels and/or combustion products. However, these studies can do no more than suggest speculative hypotheses that need to be confirmed through more rigorous research designs. Furthermore, the authors of the OEHHA document do not present the results of other research that fails to support this hypothesis.

The OEHHA document also fails to provide convincing evidence that parental exposure to benzene is associated with childhood leukemia. Only four dated, case-control studies are presented, all of which have considerable bias that might have produced spurious associations. Only two of these studies reported positive association with parental benzene exposure, one for maternal exposure and one for paternal exposure. However, these two studies conflicted with each other, reporting no increased association in the other parental sex group. Furthermore, a wider search of the literature identified four additional case-control studies addressing benzene exposure that did not report significantly increased associations. This included two very large (> 1000 case) studies that found no association.

The OEHHA report indicates that benzene exposure damages sperm under laboratory conditions, citing this as evidence for an effect from paternal exposure. However, they provide no mechanistic evidence that such sperm damage would subsequently produce childhood leukemia. Furthermore, with the exception of McKinney et al. (1991), the literature is consistent in finding no increased leukemia risk from paternal benzene exposure. This includes the original Chinese study by Shu et al. (1988) and the larger, more recent studies by Kaatsch et al. (1998) and Shu et al. (1999).

Overall, the reviewed studies provide no evidence whatsoever for an association between parental benzene exposure and childhood ALL, which is the predominant leukemia subtype (i.e. 56-88% of cases in the reviewed studies). McKinney et al. (1991) evaluated both childhood leukemia and non-Hodgkin's lymphoma together, with no separate analyses by leukemia

subtype. Shu et al. (1988) failed to find any positive association between ALL and paternal or maternal exposure to benzene, despite the fact that Chinese occupational exposures are typically much higher than those in Western countries. This finding was subsequently confirmed in a much larger US-based study (Shu, 1999).

One cannot completely discount a possible association between maternal exposure during pregnancy and ANLL, given that Shu et al. (1988) reported a significantly increased four-fold (95% CI 1.8-9.3) association with maternal benzene exposure (based on 11 exposed cases and 21 exposed controls) and a significantly increased two-fold association with gasoline exposure. However, no conclusions on the causal relationship between benzene and ANLL can be drawn from this single study, especially given the fact that Buckley et al. (1989) found no significantly increased association with maternal exposure to solvents or petroleum products. Also, Raashou et al. (2001) found no significantly increased ANLL association with community exposure to benzene during pregnancy. Although it is possible that the findings of Shu et al. (1988) reflect the very high benzene exposures experienced by Chinese workers, such highly elevated occupational benzene levels (e.g. often in the range of 10-100 ppm or more) provide little useful information regarding indirect effects from ambient exposures that are 4-6 orders of magnitude lower. Finally, none of the cited case-control studies, including Shu et al. (1988), provide evidence that postnatal childhood exposures to low levels of benzene are associated with ANLL, or that children are more sensitive to benzene exposure than adults.

Response 11-10: OEHHA thanks API for this detailed analysis of the epidemiological literature. Their analysis highlights the limitations in the human studies of early life exposures to benzene, while recognizing that there are reasons for concern regarding parental exposures to benzene. The analysis underscores why a causal relationship between benzene and childhood leukemia would be difficult to establish.

OEHHA also thanks API for identifying additional studies not cited in the draft. These studies will be reviewed in the final version of the report. The Scientific Review Panel will review these comments and responses as part if its deliberations on the prioritization process under SB25. On

the basis of this review, and the new information and analysis, the prioritization of benzene is subject to change.

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